REMARKS

In view of the following remarks, the Examiner is respectfully requested to withdraw the rejections and allow Claims 14, 15, 25, 26, and 28-34 the only claims pending and currently under examination in this application.

Formal Matters

Claims 14, 15, 25, 26 and 28-34 are pending after entry of the amendments set forth herein.

Claims 14, 26, 28 and 32 are amended.

Please cancel Claim 27 without prejudice or disclaimer.

Support for the term "antigen" in Claim 14 is found in the specification at least at page 9, beginning at lines 19, and continuing to page 10, line 10.

Support for the amendment in Claim 14 of a bacteriophage attachment site is found in the specification at least at page 4, lines 17-25.

Support for the amendment of Claim 26 is found in the specification at least at page 4, lines 17-25.

Claim 28 is amended to correct a typographical error.

Claim 32 is amended to correct antecedent basis.

These amendments add no new matter and their entry by the Examiner are respectfully requested.

Specification

The Examiner has objected to the title as allegedly not being descriptive. Without necessarily agreeing with the objection, the Applicants have amended the title.

Rejections under 35 U.S.C. §112, second paragraph

The Examiner has rejected Claims 14, 15, 25, 26, 27, 28, 29, 30, 31, 33 and 34 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite as to the term "an antigen."

Without necessarily agreeing with the appropriateness of the rejection, the Applicants have amended the claims to specify "Listeria cells that express said antigen." As such, the Applicants respectfully request withdrawal of this rejection.

Rejections under 35 U.S.C. §102(b)

The Examiner has rejected Claims 14, 25, 29, 30, 31 and 32 under 35 U.S.C. §102(b) as allegedly being anticipated under Shen et al., (Proc. Nat. Acad. Sci. USA (1995) 92:3987-3991; henceforth "Shen").

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631, (Fed. Cir. 1987). The standard for anticipation under section 102 is one of strict identity. An anticipation rejection requires a showing that each limitation of a claim be found in a single reference, *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.,* 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984). Further, an anticipatory reference must be enabling, see *Akzo N.V. v. United States Int'l Trade Comm'n* 808 F.2d 1471, 1479, 1 U.S.P.Q.2d 1241, 1245 (Fed. Cir. 1986), *cert denied*, 482 U.S. 909 (1987), so as to place one of ordinary skill in possession of the claimed invention. To anticipate a claim, a prior art reference must disclose every feature of the claimed invention, either explicitly or inherently. *Glaxo v. Novopharm, Ltd.* 334 U.S. P.Q.2d 1565 (Fed. Cir. 1995).

The Applicants have amended Claim 14 to specify that the integration vector comprises a listeriophage attachment site. Shen does not disclose this currently claimed element because Shen relies on homologous recombination for site specific integration. Because Shen does not teach this element, Shen does not disclose every element of the claims. As such, Shen does not anticipate Claims 14, 25, 29, 30, 31 and 32 under 35 U.S.C. §102(b) and this rejection may be withdrawn.

Rejections under 35 U.S.C. §103(a)

The Examiner has rejected Claims 14, 15, 25, 29, 30, 31 and 32 under 35 U.S.C. §103(a) as allegedly being unpatentable over Frankel et al., (U.S. Patent 6,099,848; henceforth "Frankel").

In order to meet its burden in establishing a rejection under 35 U.S.C. §103, the Office must first demonstrate that a prior art reference, or references when combined, teach or suggest all claim elements. S*ee, e.g., KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740 (2007); *Pharmastem Therapeutics v. Viacell et al.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007); MPEP § 2143(A)(1). In addition to demonstrating that all elements were known in the prior art, the Office must also articulate a reason for combining the elements. See, *e.g., KSR* at 1741; *Omegaflex, Inc. v. Parker-Hannifin Corp.*, 243 Fed. Appx. 592, 595-596 (Fed. Cir. 2007) citing *KSR*. Further, the Supreme Court in *KSR* also stated that that "a court *must* ask whether the improvement is more than the predictable use of prior art elements according to their established functions." *KSR* at 1740; emphasis added. As such, in addition to showing that all elements of a claim were known in the prior art and that one of skill had a reason to combine them, the Office must also provide evidence that the combination would be a predicted success.

The Applicants have amended Claim 14 to specify the integration vector comprises a listeriophage attachment site. The Applicants do not find a teaching of this element in Frankel. Frankel does not teach or suggest this currently claimed element because Frankel relies on a vector using homologous recombination to insert DNA into the Listeria genome.

Accordingly, Frankel does not teach or suggest all elements of the claimed invention. Thus, Claims 14, 15, 25, 29, 30, 31 and 32 are not obvious under 35 U.S.C. §103(a) over Frankel, and this rejection may be withdrawn.

The Examiner has rejected Claims 14, 15 and 25-32 under 35 U.S.C. §103(a) as allegedly being obvious over Frankel (referenced above) in view of Frazao et al.,

(WO99/07861, publication date: February 18, 1999; henceforth "Frazao") and Loessner et al., (Mol. Microbio. (2000) 35(2):324-340; henceforth "Loessner").

The Supreme Court in *KSR* noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Court quoting *In re Kahn* stated that: " '[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" (*KSR* at 1741) The court also stated: "As is clear from cases such as *Adams*, a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." (*KSR* at 1741)

The Applicants respectfully submit that the Office has not provided a credible articulated reason to support the legal conclusion of obviousness. The reason provided by the Office is stated on page 7 of the April 3, 2008 Office Action and reproduced below:

> immune response to antigen because Frazao et al teach that exogenous DNA can be linked to this region to provide for site-specific integration into the genome and that Frazao et al teach that the integrative vectors and the integrating process described is not restricted to mycobacteria and is specifically applicable to other bacteria such as *Listeria spp.* (page 7, first full paragraph) and Frankel et al teach that the preferred method for producing a recombinant *Listeria* having a gene encoding a heterologous antigen integrated into the chromosome thereof and that the vaccine expressing the integrated heterologous antigen can be administered to an animal so as to provide for a cellular immune response.

(emphasis added)

The Applicants assert that the Office has not articulated a credible reason as shown in the passage above to combine all three references.

As best understood, the Office's position is based on the assumption that one would inherently be motivated by Frazao to modify Frankel to use an integrase and an integrase attachment site instead of homologous recombination, and that one would

look to Loessner for a Listerophage integrase and integrase attachment site. The Applicants submit that this is not a credible reason because to do so would require one to employ the more complicated two vector plasmid method of Frazao, and then further complicate this method by using the untried and untested Listeriophage A118 integrase and integrase attachment sites from Loessner. Absent a clearly articulated reason from the Office, one of skill in the art would not combine the references, because Frankel alone teaches producing a polypeptide in Listeria via homologous recombination. One of skill in the art looking to express polypeptides in Listeria need look no further than Frankel and has no motivation to substitute Frazao's method from *M. Tuberculosis*, and then further modify that method with additional untried elements from Loessner in the hope this would provide expression in Listeria equal to Frankel.

Therefore, until the Office articulates a credible reason as to why Claims 14, 15 and 25-32 are obvious under 35 U.S.C. §103(a) over Frankel in view of Frazao and Loessner the Examiner has not made a proper *prima facie* case of obviousness and this rejection may be withdrawn.

Further, the Supreme Court in *KSR* also stated that that "a court *must* ask whether the improvement is more than the predictable use of prior art elements according to their established functions." *KSR* at 1740; emphasis added. As such, in addition to showing that all elements of a claim were known in the prior art and that one of skill had a reason to combine them, the Office must also provide evidence that the combination would be a predicted success.

The Examiner cites Loessner for the elements of an integrase and integrase attachment site from 40Kb of Listerophage sequence. The Examiner asserts that these elements can be substituted for the M6 Mycobaterial elements of Frazao.

The Loessner reference provides the A118 elements in their native form, placed within 40Kb of primary sequence and native structure. However, there is no teaching or suggestion in Frazao or Loessner that the A118 elements separated from their native context in Listeriophage A118 are capable of functioning in the artificial plasmids of Frazao in the same manner as within the 40Kb of the A118 phage genome. Nowhere

do the cited references provide that the integrase attachment site can be removed from the complete phage genome and placed on a vector and expect the attachment site to remain functional, much less provide for site specific integration.

Furthermore, published works reporting the mechanism of action for other integrases would provide one of skill in the art with doubt about whether one could remove the integrase attachment site from the phage genome and retain its functionality. Specifically, it is has been shown that the integrase for lambda bacteriophage recognizes and binds to not only the core attP sequence, but also cis sequences downstream and upstream of the core attP sequence (see Exhibit A, page 466, Figure 4). Therefore, until the Applicants showed that the attP could be separated from the genomic sequence for listeriophages, there was no reasonable expectation that the attP would remain functional after separation form the flanking sequences.

Therefore, until the Applicants showed that the attachment site could be separated from its genomic sequence for Listeriophages, there was no reasonable expectation that the attachment site and integrase would remain functional when taken out of the Listeriophage context.

Because there is no such teaching or suggestion in Loessner or Frazao, the Applicants achieving success with the Listerophage elements isolated from their native context is an unexpected result. Accordingly, one of ordinary skill in the art could not have predicted success in the claimed invention prior to the Applicant's work.

Therefore, because the Office has not put forth a credible articulated reason as to why one of ordinary skill in art would have combined the teachings in the manner put forth by the Office and one of ordinary skill in the art could not have predicted success in the claimed invention prior to the Applicants' work, Claims 14, 15 and 25-32 are not obvious under 35 U.S.C. §103(a) over Frankel in view of Frazao and Loessner, and this rejection may be withdrawn.

CONCLUSION

In view of the amendments and remarks above, this application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issuance.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number BERK-017CIP.

Respectfully submitted,

BOZICEVIC, FIELD & FRANCIS LLP

Date: July 3, 2008

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Enclosure:

- Exhibit A: Campbell et al., *Bacteriophages*, Chapter 15, FUNDAMENTAL VIROLOGY, Fields et al. (ed), 3rd Edition (1996).

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